



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|------------------------------|------------------|
| 10/068,137 | 02/06/2002 | Danilo Porro | 2027.547096/RFE (2005470) | 8385 |
| 23720 | 7590 | 12/30/2003 | EXAMINER | |
| WILLIAMS, MORGAN & AMERSON, P.C. 10333 RICHMOND, SUITE 1100 HOUSTON, TX 77042 | | | KERR, KATHLEEN M | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1652 | 10 |
| DATE MAILED: 12/30/2003 | | | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/068,137

Applicant(s)

PORRO ET AL.

Examiner

Kathleen M Kerr

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 35-42 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 35-42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6-9. 6) ☒ Other: page 53 of specification.

DETAILED ACTION

Application Status

1. By virtue of a preliminary amendment filed on February 6, 2002, Claims 1-34* have been cancelled and Claims 35-42* have been added. *Claim numbering was adjusted because the originally filed application had 34 claims, not 36 as indicated in Applicants' amendment. Thus, all previously pending claims were cancelled and added claims were renumbered starting with Claim 35. Claims 35-42 are pending in the instant application and will be examined herein.

Priority

2. The instant application is granted the benefit of priority for the foreign application MI97A002080 filed on September 12, 1997 and International Application No. PCT/EP98/05758 filed on September 11, 1998 as requested in the declaration. The instant application is also granted the benefit of the parent application 09/508,277 filed on June 29, 2000, now USPN 6,429,006 as requested in the first lines of the specification and the transmittal sheet.

A certified translation of the foreign priority document MI97A002080 has been filed.

Information Disclosure Statement

3. The information disclosure statements have been filed as follows: three on February 6, 2002 (day of filing) and one on June 11, 2002. References have been considered as noted on the attached copies; duplicate citations have been deleted by the Examiner.

Drawings

4. The drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Compliance with the Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). A paper copy and CRF of a sequence listing containing SEQ ID NOs: 1-12 was filed on March 21, 2002; while a statement of sameness was made, no statement concerning new matter was filed. Also, the following sequences are disclosed in the specification without benefit of SEQ ID NOs:

a) On page 36, several DNA sequences are disclosed without benefit of SEQ ID NOs. To be in compliance, applicants must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d).

Objections to the Specification

6. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Processes for Producing Lactic Acid using Yeast Transformed with a Gene for Lactate Dehydrogenase---

7. The specification is objected to for lacking appropriate and updated continuity data in the first paragraph. The instant application claims the benefit of U.S. Application No. 09/508,277 filed on June 29, 2000, which is now USPN 6,429,006. Moreover, claims in the parent patent are drawn to yeast strains only while claims in the instant application are drawn to methods; thus, a “continuation” application is inappropriate. The instant application must be changed to a ---divisional--- application. Appropriate amendment to the specification is required (see M.P.E.P. § 201.11).

8. The specification is objected to for containing citations of internet addresses in an improper format on page 28, line 9; page 30, line 4; page 32, line 29; and page 40, line 30 (see MPEP 707.05(e)). Appropriate correction is required.

9. The specification is objected to for having confusing stray marks. In Table C (page 53), the OD₆₆₀ and glucose columns for Rows 122.5 and 167 (Time) have a box with arrows (see enclosed copy); this inclusion is confusing. Was this some correction? Clarification is required.

Claim Objections

10. Claim 41 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Lactic acid, as required in the parent Claim 35, is found in D and L form only. Thus, limiting lactic acid to both of these two forms adds no further limitation on the scope of Claim 35.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 35-42 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 35, the clause “lacks ethanol production ability or has a reduced ethanol production ability with respect to a wild-type yeast” is redundant and confusing. Any yeast that wholly “lacks ethanol production ability” will also have “reduced ethanol production ability”, thus the second phrase is sufficient and clearer. By reciting both phrases, additional meaning that than cited above is indicated.

Moreover, the phrase “**with respect to a wild-type yeast** of the same strain which has been similarly transformed with the gene encoding lactate dehydrogenase” (emphasis added) is confusing since it implies that the transformation with LDH produces the reduced ethanol production ability. Reading the specification, this does not appear to be the intended scope of the

Art Unit: 1652

claim; however, limitations from the specification cannot be read into the claims. Are only “modified” yeasts useful in this method irrespective of the transformation with LDH? What, then, is wild-type? When reading the specification, examples use yeast strains with deleted PDC (pyruvate decarboxylase) and PDA (pyruvate dehydrogenase) genes to affect this “reduced ethanol production ability.” Is this an implied element in the claims? The exact nature of the yeast strains available for use in the claimed methods is unclear.

Overall, the claims are confusing as written. Clarification on both of the above points is required.

12. Claims 35-42 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is confusing if the requirement of the production of 0.5-1 gram lactic acid per gram of glucose is used to characterized the yeast strain, which is as written, or to characterize the step of growing. The latter seems to be more appropriate; however, for Claim 36, the yield is confusing when using a different carbon source. Clarification is required.

13. Claims 38-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The requirement of a particular pH is unclear as to whether this pH is at the beginning or the end of fermentation since fermentation greatly alters the pH of the media (see, for example Table 3). Clarification is required.

Art Unit: 1652

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 35-42 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In Claim 35, the range of “0.5 gram lactic acid per gram of glucose to 1 gram of lactic acid per gram of glucose” is not supported in the specification as originally filed (50-100% yield). The Examiner notes that Claim 35 was added to the application on the day of filing by way of a preliminary amendment; however, said amendment was not referred to in the declaration filed with the instant application (a copy of the parent declaration has been filed). Thus, the preliminary amendment is not considered a part of the original specification, but an amendment as any other.

While the specification describes the invention using yeast with high “even higher yields (>80% g/g)” (see page 5, line 20), the Examiner can find no support for any claimed range except, perhaps, in the Examples. In Table 3B and Table 7, *Kluyveromyces* BM3-12D[pLAZ10] produces as high as 75.7%, 85.4% and 88.1% yield of lactose from glucose. In Table 3B, *Saccharomyces* CENPK113ΔPDC2[pLC5-KanMX] and CENPK113ΔPDC1, Δ5, Δ6[pLC5-KanMX] have 54.9 and 50% yields of lactose from glucose, respectively. In Table 6, *Kluyveromyces* PMI/C1[pEPL2], under extended fermentation (137 hours) produces 59% yield. Nowhere is 90% or 100% achieved. Thus, the range of 50-100% is not supported in the

Art Unit: 1652

specification as originally filed. Applicants must cite clear (page and line number) support for the amendment or it must be deleted from the application. Correction/clarification is required.

15. Claims 35-42 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for producing particular levels of lactate at particular pHs, does not reasonably provide enablement for producing 100% lactate from glucose at infinitely low pHs (see Claims 38-40). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or practice the invention commensurate in scope with these claims. One of skill in the art would be required to perform undue experimentation to make and/or practice the invention to the full extent of the claimed scope.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

Art Unit: 1652

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Applicants have provided no guidance or working examples of how to achieve high yields (90-100%) of lactate with their disclosed yeast strains or how to practice the claimed methods at infinitely low pHs. The nature of the high yielding yeast strain is such that it is unlikely that excessively high amounts of lactate can be produced in yeast strains, having a toxic pH effect; the nature of the processes at very low pHs is that very few organisms grow outside normal pH ranges. It is wholly unpredictable, considering the disclosure and the prior art together, to be able to adjust the disclosed yeast strains to produce extremely high amounts of lactate or to be able to adjust the processes disclosed to achieve very low pH levels and still produce lactate. Thus, the instant claims are not enabled to the full extent of their scope.

The Examiner notes that pH control seems to be the only substantive difference between Porro *et al.* (1995) (see discussion of Closed Prior Art below) and the claimed invention. Porro *et al.* (1995) use LDH expression in a PDC minus yeast but produce little lactic acid when pH is uncontrolled during lactic acid production (see pages 294-295-bridging paragraph and page 296, right column). Since three inventors are also authors of Porro *et al.* (1995), additional comments on the discrepancies of Porro *et al.* with respect to the instant invention are requested.

16. Claims 35-42 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods of producing high yields of lactic acid using yeast strains with reduced pyruvate decarboxylase activity and optionally reduced pyruvate dehydrogenase activity, does not reasonably provide enablement for methods of

Art Unit: 1652

producing high yields of lactic acid using yeast strains with reduced ethanol production ability via some other structural feature. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. One of skill in the art would be required to perform undue experimentation to make and/or practice the invention to the full extent of the claimed scope.

The factors to be considered in determining whether undue experimentation is required are summarized above.

To practice the full scope of the claimed invention, one of skill in the art would be required to produce the key reagent in the claims, the yeast strains having reduced ethanol production ability. On pages 8-9 of the instant specification, numerous examples of yeast with reduced ethanol production ability are described. All of these have reduced/deleted PDC (pyruvate decarboxylase) activity and optionally reduced/deleted PDA (pyruvate dehydrogenase) activity. Thus, the specification enables the use of these yeasts since adequate structure/function has been disclosed. However, the specification does not generally describe structural features, outside of those above, that lead to reduced ethanol production ability in yeasts. To practice the claimed invention, one of skill in the art, then, would be required to make such yeasts absent any direction. While this feature is within the skill of the art to be screened for, the ability to “find” is not equivalent to the ability to “make” as required by the statute. The art provides little direction for production of such yeasts. The ability to make such yeasts is wholly unpredictable. Thus, the instant claims are not enabled for the full extent of their scope.

Art Unit: 1652

Closest Prior Art

17. The following is a description of related prior art:

- a) Dequin *et al.* (WO 94/00554 – see IDS) teaches transformation of *S. cerevisiae* with an LDH gene from *L. casei* for the production of lactate with a yield of 25-30%; this yield is less than the noted range of 50-100% and the *S. cerevisiae* host cells also do not have the limitation of reduced ethanol production ability.
- b) Porro *et al.* (1995 – see IDS) teach *S. cerevisiae* GRF18 transformed with a bovine LDH gene can produce 50-70% yield lactic acid when the growth media carbon source is manipulated (see page 296, right column). However, GRF18 lacks the reduced ethanol production limitation.

Porro *et al.* also teach the desire to reduce ethanol production in yeast harboring an LDH gene for the production of lactic acid. Porro *et al.* attempt this combination by transforming *S. cerevisiae* YSH 5.127-17 (a deleted *pdcl*, *pdc5*, and *pdc6* yeast strain) with a bovine LDH gene; however, the lactate production is “low” and not reported (see page 296, left column). Porro’s using YSH 5.127-17 is very similar to Applicants’ using *S. cerevisiae* CENPK113PDCΔ1,Δ5,Δ6[pLC5-KanMX] to produce a 50% lactate yield, the difference being that Applicants’ LDH gene is from *L. casei* and said gene is on an integrating vector as opposed to the replicative vector with bovine LDH of Porro *et al.* Thus, a case for inherency cannot be made that the teachings of Porro *et al.* would produce a 50% yield of lactate.

Conclusion

18. Claims 35-42 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Kathleen M Kerr
Examiner
Art Unit 1652

December 20, 2003